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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,572	10/30/2003	Masataka Andoh	068454-0102	5923

22428 7590 05/17/2007

FOLEY AND LARDNER LLP  
SUITE 500  
3000 K STREET NW  
WASHINGTON, DC 20007

EXAMINER
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NEGIN, RUSSELL SCOTT

ART UNIT	PAPER NUMBER
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1631

MAIL DATE	DELIVERY MODE
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05/17/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

Application No.

10/696,572

Applicant(s)

ANDOH ET AL.

Examiner

Russell S. Negin

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 15 February 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 4, 16, 29, 30 and 32-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-15, 17-28 and 31 is/are rejected.
- 7) ☒ Claim(s) 5 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 July 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Comments***

Applicants' amendments and request for reconsideration in the communication filed on 15 February 2007 are acknowledged and the amendments are entered.

Claims 1-34 are pending in this Office action.

Claims 1-3, 5-15, 17-28, and 31 are examined in this Office action.

Claim 4 has a status identifier "Withdrawn." "Withdrawn - Currently amended" would be more appropriate (see 37 CFR 1.121). The amendment has been entered nonetheless.

### ***Specification***

The objection to the disclosure because of informalities from the previous Office action is withdrawn due to amendments made by applicant to the specification filed on 15 February 2007.

### ***Claim Objections***

The objection to claim 12 in the previous Office action because of informalities is withdrawn due to amendments made by applicants to the claim filed on 15 February 2007.

The following objection is newly applied:

Claim 5 is objected to because of the following informalities:

Claim 5 ends with the phrase "the gene expression intensity data of all spots has been standardized," which should read, "the gene expression intensity data of all spots have been standardized."

Appropriate correction is required.

### ***Drawings***

The amendments to the drawings filed on 1 July 2004 are objected to because they are not labeled "Replacement Sheet" or "New Sheet." Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-15, 17-28, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following 35 U.S.C. 112 Rejections are newly applied:

Claims 1-3, 5-15, 17-28, and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 (line 5), claim 13 (line 5), claim 26 (line 5), and claim 27 (line 5) the term "previously adjusted" is used to describe gene expression. The term "previously adjusted" is a relative term which renders the claim indefinite. The term "previously adjusted" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear when, and to whom or where the gene expression is "previously adjusted." The set of claims are consequently indefinite.

Claims 2, 7-8, 10, 14, and 19-20 recite the phrase "the distortion." The independent claims to which they refer recite both local and global distortions and it is consequently unclear as to which type of distortion is being analyzed.

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Claim 3 recites the limitation "the order statistics" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 recites the limitation "the order statistics" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 28 recites the limitation "the order statistics" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 31 recites the limitation "the order statistics" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 11 and 24-25 recite the use of "the correction." However, it is unclear and indefinite as to whether a first or second correction means is indicated (the independent claims recite two separate correction means).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-15, 17-28, and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for S-D (second-derivative) transformations via related prior art, does not reasonably provide enablement for the S-D transformations which result in the plots generated in the instant application. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must identify and use an S-D transformation as indicated in the drawings. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The description of the invention illustrates S-D plots in the drawings, but does not explicitly dictate what an S-D transformation is either physically or mathematically in order to be able to properly interpret the drawings.

c) The disclosure does not provide working examples of S-D transformations. Again, while S-D plots are illustrated there is no example providing the mathematical guidance of how these plots were generated.

d) The nature of the invention, S-D transformations for better analysis of microarray data, is complex.

e) The prior art does not show S-D transformations as intended in the drawings. Hiyama et al. (International Journal of Oncology, volume 27, pages 87-95, 2005-

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published two years after the effective instant priority date) describes S-D

transformations in the caption to Figure 1 in column 1 of page 88:

Figure 1: The two-dimensional mixed normal model with four components for S-D plot proposed by Ohtaki et al. (23) is shown schematically...

While this passage recites S-D plots for use in microarrays, it also states that S-D plots were proposed by Ohtaki et al. in reference #23. The citation of reference #23 indicates that this reference was not published until 2004, a year after the priority date of the instant application. Consequently, S-D transformations, as used in the instant application were not present in the art prior to the priority date of the instant application.

Instead, the prior art illustrates S-D product transformations as a "second derivative transformation" in normalizing microarray data as shown in paragraphs [0064] – [0070] of Weng [US PGPUB 2003/0226098].

f) The skill of those in the art of S-D transformations is high.

g) The predictability of S-D transformations as intended in the drawings is unknown in the prior art. Page 6, lines 4-8 state:

An S-D plot-based correction unit for a third process involves an S-D transformation, which is a variation of an MA transformation (for information about the MA transformation and an MA plot, refer to the above nonpatent document 6).

While nonpatent document 6- Yang et al. [Nucleic Acids Research, February 2002, vol 30, e15, 10 pages] describes MA plots, Yang et al. does not describe how MA plots are related to S-D plots. It is unpredictable from the prior art the result of an S-D transformation.

h) The claims are broad in that they are drawn to any method of normalization which includes an S-D transformation.



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The skilled practitioner would first turn to the instant description for guidance in using the claimed invention. However, the description lacks clear guidance on S-D transformations. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not discuss S-D transformations. Finally, said practitioner would turn to trial and error experimentation to determine S-D transformations. Such amounts to undue experimentation.

***Claim Rejections - 35 USC § 102***

The rejection of claims 1, 2, 6, 13, 14, 26, and 27 under 35 U.S.C. 102(b) as being anticipated by Yang et al. [Nucleic Acids Research, February 2002, vol 30, e15, 10 pages] is withdrawn due to arguments made by applicants on pages 15-18 of the Remarks of 15 February 2007.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

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under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 13-14, and 26-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. [Nucleic Acids Research, 2002, volume 30, page e15, 10 pages] in view of Weng [US PGPUB 2003/0226098].

Claim 1 is drawn a cDNA microarray data correction system for correcting global an local distortions of microarray data and correcting measurement errors caused by a difference in sensitivity between fluorescent dyes comprising five steps.

The preamble of claim 1 is taught in the first two sentences of the abstract of Yang et al. which states:

There are many sources of systematic variation in cDNA microarray experiments which affect the measured gene expression levels (e.g. differences in labeling efficiency between the two fluorescent dyes). The term normalization refers to the process of removing such variation.

The first step of the body of instant claim 1 states gene expression intensity data is input and background noise is removed. The passage under "Image processing" in column 2 of page 2 of Yang et al. states:

Each hybridization produced a pair of 16-bit images, which were processed using the software package Spot. The main quantities of interest produced by the image analysis methods (segmentation and background correction) are the (R,G) fluorescence intensity pairs for each gene on each array (where R = red for Cy5 and G = green for Cy3). Note that we call the spotted DNA sequences 'genes,' whether they correspond to actual genes, ESTs or DNA sequences from other sources.

The second step of data standardization using grid-by-grid order statistics for inputting and transmitting gene expression data is described at the top of page 3,

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column 1 of Yang et al., which is entitled, "Within-print tip group normalization" and is based in part on grid data. The model listed is used to input and transmit data.

The third step of instant claim 1 is a first correction means for performing a distortion depending on a spot position on grid coordinates for the standardized gene expression intensity data. The "Scale normalization" section in column 1 (line 8) of page 3 of Yang et al. teaches such a normalization. The equations in this section illustrate a nonparametric smoothing method.

The fourth step of instant claim 1 is a second correction means for performing a distortion depending on a spot position on grid coordinates for the standardized gene expression intensity data. The "Composite normalization" section in column 1 (line 8) of page 3 of Yang et al. teaches such a second correction means. In addition, the "Intensity-dependent normalization" at the bottom 10 lines of column 2 of page 2 of Yang et al. describes the use of MA plots (i.e. output) and could also serve as a second correction means for the data.

However, the article of Yang et al. does not teach S-D transformations.

The application of Weng, entitled "Methods for analysis of measurement errors in measured signals" performs second derivative transformations to analyze microarray data (see paragraphs [0064] to [0070]). The purpose of the application of Weng is described in paragraph [0010] which states:

The present invention provides methods for analyzing measurement errors in measured signals obtained in an experiment, e.g. measured intensity signals obtained in a microarray gene expression experiment or microarray proteomics experiment. Signals from any experimental measurement can be analyzed by the methods of the present invention.

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It would be obvious for someone of ordinary skill in the art at the time of the instant invention to modify the microarray normalization methods of Yang et al. by use of the microarray signal transformations of Weng because while Yang et al. transforms and plots the experimental data according to the theories proposed, Weng has the advantage of using the required S-D (second derivative) transformation for the ability to better analyze microarray signal data.

Related transformations are plotted in the Figures 1-4 of Weng (the additional limitation of instant claim 2 is a plot of the S-D transformation).

It would be obvious for someone of ordinary skill in the art at the time of the instant invention to modify the microarray normalization methods of Yang et al. by use of the microarray signal transformations of Weng because while Yang et al. transforms and plots the experimental data according to the theories proposed, Weng has the advantage of using the required S-D (second derivative) transformation for the ability to better plot error in microarray signal data.

Instant claim 13 is drawn to a species of instant claim 1 with several intermediate outputting steps after each transformation.

It would have been obvious to someone of ordinary skill in the art to repetitively output results of each intermediate transformation because it is obvious to repeat the steps of a claim. In this instance, instant claim 1 outputs results as a final step. It is obvious to repeat this step of outputting the results at various points in the claim because there is no mandating of the order in which to carry out the steps of instant claim 1. In other words, instant claim 1 can be repeated multiple times with the

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outputting steps at each of the same locations of the outputting steps in instant claim 13 and make obvious instant claim 13 over the prior art used for instant claim 1.

Related transformations are plotted in the Figures 1-4 of Weng (the additional limitation of instant claim 14 is a plot of the S-D transformation).

It would be obvious for someone of ordinary skill in the art at the time of the instant invention to modify the microarray normalization methods of Yang et al. by use of the microarray signal transformations of Weng because while Yang et al. transforms and plots the experimental data according to the theories proposed, Weng has the advantage of using the required S-D (second derivative) transformation for the ability to better plot microarray signal data error.

Instant claims 26-27 are drawn to the same method steps as instant claim 13 with the additional limitations of claims 26-27 having preambles indicating the method is a DNA microarray data correction program, and a computer readable medium containing the DNA microarray data correction program, respectively.

Weng discloses a computer with computer readable media in Figure 14.

It would be obvious to someone of ordinary skill in the art at the time of the instant invention to modify Yang et al. in view of the automated method of Weng because Weng can carry out the method expeditiously and accurately on a computer system.

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***Response to Arguments***

Applicant's arguments filed 15 February 2007 have been fully considered, and they are persuasive. New grounds of rejection have been applied.

***Conclusion***

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

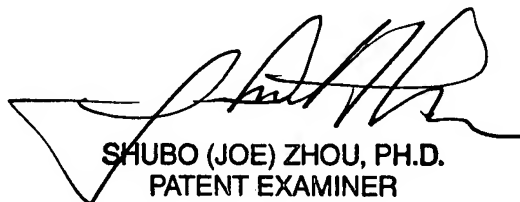
If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Ram Shukla, Supervisory Patent Examiner, can be reached at (571) 272-0735.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RSN

10 May 2007

*R 5/10/07*

  
SHUBO (JOE) ZHOU, PH.D.  
PATENT EXAMINER